

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number  
WO 01/03664 A1

- (51) International Patent Classification<sup>7</sup>: A61K 7/48, 31/375, A61P 17/00 (74) Agent: HALVORSON, Kristofer, E.; The Halvorson Law Firms P.C., Suite 1, 405 W. Southern Avenue, Tempe, AZ 85282 (US).
- (21) International Application Number: PCT/US00/18392
- (22) International Filing Date: 1 July 2000 (01.07.2000) (81) Designated States (national): CA, JP.
- (25) Filing Language: English (84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
- (26) Publication Language: English
- (30) Priority Data: 09/349,324 8 July 1999 (08.07.1999) US Published:  
— With international search report.  
— Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- (71) Applicant: INTERNATIONAL FLORA TECHNOLOGIES, LTD. [US/US]; 1151 North Fiesta Boulevard, Gilbert, AZ 85233-2238 (US).
- (72) Inventors: KLEIMAN, Robert; 7129 E. Laguna-Azul Avenue, Mesa, AZ 85208 (US). BROWN, James, S.; 2200 W. San Angelo #3059, Gilbert, AZ 85233 (US). For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/03664 A1

(54) Title: STABILIZED ASCORBIC ACID, COMPOSITION, AND METHOD OF USE

(57) Abstract: A stable composition for the delivery of vitamin C comprises particles of vitamin C (including its pharmaceutical or cosmetic derivatives) dispersed in a solid phase of wax that is chemically inert to the vitamin C. The proportions of the jojoba esters should be chosen to provide the dry-feel to the composition that is highly desired. This will usually require at least 10 %, and most preferably at least 60 % by weight of carrier material (excluding solvent and actives) in the composition. The ingredient must be contained in at least the amount needed to be effective, which in the case of vitamin C is at least 5 % (e.g., at least 5.5 % or at least 6.0 % by weight), preferably at least 10 % by weight of the dispersion/suspension as the water-soluble material or water-dispersible material.

**STABILIZED ASCORBIC ACID, COMPOSITION, AND METHOD OF USE**  
**BACKGROUND OF THE INVENTION**

**TECHNICAL FIELD OF THE INVENTION**

The present invention relates to a method for stabilizing vitamin C (ascorbic acid and its derivatives), a method of manufacturing materials with stabilized vitamin C (ascorbic acid and its derivatives therein), and materials useful as emollients or components of cosmetic or topically applied pharmaceuticals with stabilized vitamin C or its derivatives therein. The materials of the invention may be provided as particles that contain stabilized vitamin C. The particles are particularly useful in the cosmetic, dermatological, medical and/or veterinary fields. The present invention also describes methods for using these dispersions in the cosmetic or pharmacological treatment of the skin as well as for the preparation of a cream or ointment intended for the cosmetological or dermatological treatment of the skin and/or for veterinary treatments.

**BACKGROUND OF THE ART**

Workers have long sought to stabilize vitamin C (ascorbic acid and its derivatives) in suitable pharmaceutical forms to enable wider use of its beneficial properties.

Ascorbic acid has many known biological functions, such as the stimulation of collagen synthesis, the strengthening of skin tissues against external attack (UV radiation, pollution), reduction in loss of pigmentation, activity against free radicals and compensation for vitamin B deficiency. Some of these beneficial properties have been reported in particular by England and Seifter in the article "The Bio-Chemical Functions of Ascorbic Acid" published in *Ann. Rev. Nutri.*, 1986, 6, pp. 365-406.

However, the chemical structure (alpha-keto lactone) of vitamin C (as used herein the term vitamin C and ascorbic acid and its derivatives will be used interchangeably) is very sensitive to the influence of environmental parameters such as light, oxygen, and water (due to ascorbic acid's pH sensitivity and due to the presence of trace metals in water that may form chelates with the ascorbic acid). A heretofore unavoidable degradation of ascorbic acid in aqueous solution therefor occurs over time in compositions containing ascorbic acid. The sensitivity of ascorbic acid actually allows for its use as an antioxidant stabilizer for other compositions, as the ascorbic acid is often preferentially oxidized before other materials in a

RECEIVED

MAR 3 1 2003

OFFICE OF PETITIONS

RECEIVED  
MAR 0 1 2003  
OFFICE OF PETITIONS

composition.

The problem of ascorbic acid sensitivity has been addressed in a variety of ways in the art. For example, to reduce or delay the degradation of ascorbic acid in solution, US Patent No. 5,140,043 recommends stabilization by introducing ascorbic acid into aqueous-alcoholic solutions, formed of at least 80% water and having a pH below 3.5. The high acidity of these solutions reduces or negates their utility in the cosmetic and/or pharmaceutical field. Repeated applications of such solutions could disrupt the equilibrium of the skin and might irritate, or even burn, the skin.

B.R. Hajratwala, in "Stability of Ascorbic Acid", published in the Revue Sciences Pharmaceutiques on 15 Mar., 1985, teaches that ascorbic acid may be stabilized as an acidic aqueous solution by adding a surface-active agent that is an oxyethylenated sorbitan ester. In particular, Hajratwala states that at pH=3.4 and 25 °C, the addition of this agent reduced the rate of oxidation, and thus the rate of degradation, of ascorbic acid in solution. Hajratwala also teaches the use of a chelating agent (e.g., for monovalent cations) such as ethylenediaminetetraacetic acid (EDTA) and packaging under nitrogen, in the absence of light, to enhance the stability of an aqueous ascorbic acid solution. Again, however, such an acidic aqueous solution if applied to the skin, would have the same drawbacks as those described above for acidic aqueous-alcoholic solutions. Furthermore, the stabilization provided would be insufficient for long term stability as desired in the art.

Other ways of stabilizing ascorbic acid have been proposed, in particular by a coating technique (FR-A-1,600,826) or by granulation of ascorbic acid (JP-A-53-127,819) for the agriculture-foods industry. However, these techniques tend to be expensive and may damage the ascorbic acid, for example, during heating suggested for some of the processing, and/or may lead to compositions of poor cosmetic acceptability, as in the case of granules.

FR-A-1,489,249 discloses the use of metal salts of phosphorylated ascorbic acid, in particular magnesium ascorbylphosphate, in cosmetic compositions. The latter compound has an activity close to that of ascorbic acid, from which it is derived, but it has certain drawbacks that render its use on the skin less desirable. In particular, since magnesium ascorbylphosphate is only stable at basic pH (pH 8 to pH 9), it must be incorporated into a basic composition that may be an irritant to the skin (the pH of which is about 5.5).

U.S. Patent No. 5,308,621 describes a composition for use in the transdermal

administration of ascorbic acid (vitamin C) comprising a pharmaceutically acceptable carrier having 1 to 60% by weight of ascorbic acid in suspension within the carrier, the suspension of ascorbic acid comprising fine particles of ascorbic acid sized below 20 microns, preferably between 2 and 10 microns. The composition is formed by mixing the ascorbic acid into the carrier, heating up the mixture to dissolve the vitamin C, then cooling the solution to precipitate the vitamin C as small crystals. Typical carriers include polyhydric alcohols, alcohols, polyalkylene glycols, ointment bases such as petroleum jelly and lanolin, and the like. The preferred compositions are essentially water free, with less than about 0.5% by weight water.

10 U.S. Patent No. 5,409,693 describes the use of ascorbic acid in the form of a fat-soluble fatty acid ester to treat sunburn and prevent sunburn damage to skin. The ascorbic acid derivative may be dispersed or dissolved in a pharmaceutically acceptable carrier.

U.S. Patent No. 5,552,446 describes the use of a water in oil emulsion containing stabilized ascorbic acid. The emulsion contains an aqueous phase with a pH that is at most 15 3.5 (an acidic phase) in combination with particular emulsifying agents selected from dimethiconecopolyol or alkyldimethiconecopolyol. The stabilized ascorbic acid in the emulsion is suggested for use in the cosmetic, dermatological and/or veterinarian fields. The emulsion is taught to contain at least 60% by weight of water to prevent release of oil from the emulsion that would destabilize the emulsion. The ascorbic acid content is 0.5 to 5% by 20 weight. With a maximum of 5% ascorbic acid it is limited because higher concentrations are desirable (see 5,140,043; column 3, line 22).

The present general objective for stability in the industry is represented by a goal of at least 90% residual vitamin C after one year. Magnesium ascorbyl phosphate provided by BASF Corp. is stable (more than 90%) after 55 days. This product is stable in neat form, but 25 may not be stable in formulations. It is also desirable to provide a system that can be set in a gel and/or placed into water with stability for 6 months to 1 year.

A chief use of emollients is to provide vehicles for lipid-soluble drugs (as in balms, ointments and alcohol-based liniments). Although it has often been suggested that such emollient vehicles facilitate the transport of such drugs through the skin, it has been found 30 that when the oil:water partition coefficient is greater than 1.0, the penetration of lipid-soluble drugs tends to be impeded. Emollient substances are commonly employed in cleansing and

antiphlogistic creams and lotions. Compound ointment bases, creams, and other medical applications are also general areas of use for emollients. Amongst the more common emollient materials are castor oil, corn oil, cottonseed oil, rose water ointment, apricot kernel oil, avocado oil, grape seed oil, hazelnut oil, olive oil, sesame oil, theobroma oil, almond oil, myristyl alcohol, and recently other natural oils such as jojoba oil.

Other ingredients that have been used as emollients include a number of fatty acids derived from either plants or animal sources. Fatty acids generally comprise aliphatic hydrocarbon or other organic chains with carboxylic substituents on them, typically having between 8 and 24 carbon atoms in the chain backbone. Fatty acids are often used in creams, lotions, shaving creams, lipsticks and as pressing agents in pressed powders and blushes. Fatty acids that are used in cosmetics formulations generally include at least stearic acid, oleic acid, myristic acid and palmitic acid. Other typical fatty acids include linoleic acid, behenic acid, and other common fatty acids of the general formula  $C_nH_{2n+1}COOH$ .

Fatty alcohols are also used as emollients. They are said to be less sticky and less heavy than many other fatty materials, such as the fatty acids, and are frequently used to improve the viscosity and stability of lotions and creams. They also have utility in reactive hair dying and perming products. Examples of fatty alcohols that find use in the field of cosmetics and personal care products are cetyl alcohol, lauryl alcohol, stearyl alcohol and oleyl alcohol.

Additional examples of emollients are fatty esters. One of the best qualities of fatty esters is that they do not feel as oily to the touch as some other types of emollient fatty ingredients. Examples include isopropyl palmitate, isopropyl myristate and glyceryl stearate.

An important emollient is jojoba oil, which is extracted from the seed of the species *Simmondsia chinensis*. Jojoba oil is a seed oil with excellent skin feel. The oil is composed almost exclusively of wax esters, with little or no triglycerides present. A major portion of the production of jojoba oil is used by the cosmetic industry as an emollient in a variety of products.

One of the problems with typical emollients is that the emollient itself provides a wet or oily feel to the applied areas. This can lead to an uncomfortable feeling or appearance to the user, which is very important in the cosmetic and pharmacological industry. An additive for cosmetic, personal care and topical treatment (medicament) products has been marketed

under the name of "Confetti"<sup>TM</sup> (with different alphanumeric identifiers as to specific ingredients, e.g., Confetti<sup>TM</sup> AL with allantoin, and Confetti<sup>TM</sup> EA, MT, PA, RG and SG identifying the color of the material). This material is advertised as decorative microcapsules that contribute beneficial moisturizing and delivery of alcohol soluble ingredients to the skin.

- 5 Confetti<sup>TM</sup> is advertised as having a good balance of structural integrity and rub-in characteristics, rubbing into the skin completely without any extra pressure. The Material Safety Data Sheets (MSDS) on Confetti<sup>TM</sup> products identifies them as containing a natural oil (e.g., coconut oil, tocopheryl acetate, retinyl palmitate), propylene glycol, synthetic beeswax, petrolatum, allantoin, PVM/MA Decadiene crosspolymer and benzophenone, as well as
- 10 pigments and/or dyes.

It is desirable to be able to provide vitamin C and its derivatives in a composition that is both stable against environmental or ambient factors and that can be readily applied to the skin or hair of a subject.

#### SUMMARY OF THE INVENTION

- 15 The present invention provides a method for providing a stable composition comprising ascorbic acid and/or its biologically active derivatives for use in various fields of technology, including, but not limited to the cosmetic or medical fields. The stable composition may comprise a wax, particularly a wax particle, having particles of the ascorbic acid (and/or its derivative) dispersed within the wax. The composition may be provided as an
- 20 emollient.

- Emollients tend to be bland, fatty, oleaginous substances that may be applied locally to the skin, mucous membranes, or abraded tissue. One of the benefits of emollients is their ability to exclude water-soluble irritants, air, and air-borne bacteria when a layer of emollient is present. At the present, there are numerous ingredients that function as emollients in a
- 25 wide variety of products, and which ingredients may act in subtly different ways. For example, certain emollients sit on the surface of the skin and serve to impede water loss from the skin. Such ingredients are generally comprised of large molecules that form a hydrophobic barrier to help prevent water from leaving the surface of the skin. Examples of such emollients are lanolin, mineral oil, silicone derivatives and petroleum jelly.

**DISCLOSURE OF INVENTION AND  
BEST MODE FOR CARRYING OUT INVENTION**

The present invention describes a solid carrier system for use with vitamin C and/or its biologically active derivatives, the system comprising the solid particles of vitamin C physically mixed and dispersed in wax. The wax is preferably a non-polar wax (e.g., paraffin or other hydrocarbon wax) and free of water (e.g., less than 1% total weight of particle, preferably less than 0.5%, less than 0.2%). Although not essential to the practice of the invention, the wax carrier should not dissolve the vitamin C (e.g., the vitamin C should not be soluble in the wax in an amount above 5% by weight of the wax, preferably in an amount of less than 2%, more preferably less than 1% by weight of wax at room temperature. The vitamin C need not be and preferably is not soluble in the wax at the softening point or melting point of the wax). The vitamin C may be dispersed mechanically or dissolved or partially dissolved in a solvent and then recrystallized in the wax. The particulate vitamin C must be present in the final product. Particles of the wax and stabilized vitamin C system are preferably provided with diameters between 200 and 2000 microns. The particles of the vitamin C itself is preferably particles of less than 10 microns, less than 8 microns, less than 5 microns and/or less than 3 or less than 1 microns (with dimensions down to about 0.1 microns or 0.5 microns). A preferred embodiment is the provision of the vitamin C in a wax comprising a unique product derived from jojoba oil.

Jojoba ester compositions have been found to function well as a dry carrier or vehicle for the application of active materials to the skin or hair of customers. These esters have been found to be useful in pure or blended forms as carriers or vehicles in the personal care, cosmetic, and/or pharmaceutical fields of use. The esters to be used may be provided with a range of properties (from the composition of the ester itself or from additives and blended materials) and can provide improved feel when used with other conventional carriers, vehicles, bases, actives and additives. These unique esters are described in commonly assigned U.S. Patent Application U.S. Serial No. 09/010736, filed on January 22, 1998. Upon application and 'rubbing in' of the compositions, the jojoba ester based compositions leave the skin feeling soft (which is typical of high quality emollients), yet provide a mildly persistent coating that carries the actives without leaving a wet or oily feel to the skin of the user.

The embodiment of the present invention utilizing the unique esterified jojoba oil

derivative describes a very effective dry-feel emollient composition additive for use in personal care, cosmetic and pharmaceutical products and a method of producing those products in combination with an ascorbic acid and pharmaceutically acceptable ascorbic acid derivatives in a stable composition. Typical ascorbic acid derivatives comprise esters or salts of ascorbic acid, are well known in the art. Such esters and salts include, for example, alkyl esters of ascorbic acid (e.g., ascorbyl palmitate, ascorbyl stearate, ascorbyl behenate, tetrahexyldecyl ascorbate, and the like). The composition (with the term "an ascorbic acid" or "a vitamin C" being used hereinafter as a generic term for ascorbic acid and all of its acceptable derivatives and the terms "ascorbic acid" and "vitamin C" being used to describe the specific compound) is essentially solid at room temperature, can be provided in various shapes and sizes (especially as spheres), and can be produced from saturated, partially saturated, and/or unsaturated combinations of fatty alcohols, isopropyl esters and wax esters obtained from the oil contained in the seed of the jojoba plant (*Simmondsia chinensis*), jojoba oil.

These new emollient compositions preserve the excellent skin feel attributed to jojoba oil, which has long been used as an emollient and additionally provide a vitamin C available for direct topical application to the skin from the storage stable emollient composition. These new compositions also increase the range of applications for cosmetic compositions through an emollient that is more polar and hydrophilic than is found in jojoba oils, (which may also be referred to in the art as jojoba wax esters). The composition forms physically stable emulsions much more readily than does jojoba oil. The composition may also further provide excellent emolliency to normally dry cosmetic systems involving high levels of pigments, with the emollient acting as a pigment wetting agent and as an aid to a smooth and even application of the dry system. The composition also functions as an excipient in pressed powder.

The saturated, partially saturated, and/or unsaturated compositions comprising fatty alcohols, isopropyl esters and jojoba wax esters (jojoba oil) may be obtained by the base catalyzed alcoholysis reaction between jojoba oil, or its derivatives, and an alkyl alcohol. In the alcoholysis reaction, examples of the base catalyst materials include, but are not limited to metal alkoxides and especially alkali metal alkoxides, inorganic hydroxides, especially alkali metal hydroxides, and the like such as  $\text{NaOCH}_3$ , sodium methoxide,  $\text{NaOCH}_2\text{CH}_3$ , sodium

ethoxide (potassium, calcium and lithium counterparts), KOH & NaOH (e.g., anhydrous alkali metal hydroxides in alcohol solution, with the alcohol of the solution being the alcohol used in the reaction).

Jojoba oil and its derivatives comprise a family of wax esters that have melting points  
5 that range from 10 to 71 °C. At room temperature (~20 °C), this family of esters varies from pourable liquids, to soft creams, to pasty waxes, to a brittle hard wax. Jojoba esters may be used individually or can be blended with the different melting point esters within the family to form products with selected melting points and specific physical properties or feel. These esters, whether exclusively jojoba esters or when combined with other carrier and vehicle  
10 components (including other emollients or binders) can form excellent carrier and vehicle or delivery compositions for use in the cosmetic, personal care and/or pharmaceutical field, including the cosmeceutical field where cosmetic compositions also provide pharmaceutical or other therapeutic benefits. Typical materials with which the jojoba esters may be blended in accordance with the practice of the present invention, in addition to the required inclusion  
15 of ascorbic acid in the composition, include active materials and aesthetic materials (some of which materials may bridge both groups). These materials include, but are not limited to aesthetic materials such as colorants (especially colorants of dyes or pigments that do not persist on application to a subject, but merely decorate the commercial product) and fragrances (which may also be active, as when used in aromatherapy). Active materials  
20 include, but are not limited to, cosmetic oils and waxes (both natural and synthetic, including hydrogenated or partially hydrogenated oils, vegetable oils (e.g., carrot oil), marine oils such as squalane, silicone oils, mineral oils, and long chain esters), antibacterial agents, antifungal agents, antimicrobial agents in general, tooth and gum treatment materials, analgesics, topical anesthetics, skin coloring agents (e.g., skin whitening agents), sun blocks (organic or  
25 inorganic ultraviolet radiation absorbing compounds), pesticides, insecticides, repellants, other vitamins (especially vitamin E), hormones, proteins, long chain fatty acids, alcohols, cosmeceuticals, pigments, botanical extracts, esters and ethers, dimers, trimers, oligomers, and polymers, and the like. Any new types of topical treatments or materials developed in the future would be reasonably applied by the emollient compositions of the present invention.  
30 These blended compositions may of course be combined with the active ingredients intended to be delivered by the compositions used in the present invention. The proportions of the

jojoba esters should be chosen to provide the dry-feel to the composition that is highly desired. This will usually require at least 10%, often at least 20%, preferably at least 30%, more preferably at least 40 or 50%, by weight, and most preferably at least 60, at least 70, at least 80, and at least 90% (up to 100% by weight) by weight of carrier material (excluding  
5 solvent and actives) in the composition.

The dry-feel compositions of the present invention may be applied to the skin as particulate materials, usually in a cosmetic, personal care, cosmeceutical or pharmaceutical composition. The processes of making the particles generally provides them as spherical or oblong particles, but they may be shaped by pressing, molding, spray drying, atomization or  
10 other stresses to provide shaped particles, including platelets. The jojoba esters have particular properties that renders them especially suitable for use in fragrance dispensing compositions and topical applications, and those properties include their spreadability, emolliency, non-volatility, lack of color and lack of odor. The lack of odor is mildly important in pharmaceutical applications, but is viewed as particularly essential in the  
15 provision of fragrances. Perfume and cosmetic providers have extremely rigid standards on non-essential odor contribution in their products.

By skillful blending, a mixture of jojoba esters with the vitamin C (as well as with other optional additives such as fragrance oils) can be prepared that melt at slightly below skin temperature. When formed into spherical particles and rubbed into the skin, these  
20 spherical particles disappear into the skin. Indeed they soften, melt and are adsorbed onto the surface of the skin where they deposit a layer of the jojoba esters containing vitamin C and fragrance. Jojoba esters are non-volatile and form an imperceptible film on the skin that slows down the release of the fragrance and at the same time provide a slow release "patch" effect for the vitamin C. These jojoba esters, being low in odor and superior skin emollients,  
25 provide an excellent carrier and delivery system for vitamin C as well as for fine fragrances.

Spheres formed from the present invention that contain fragrance or perfume, in addition to vitamin C, can be incorporated into a larger variety of cosmetic and personal care products for the purpose of providing emolliency to the skin. At the same time, these fragrances bearing spheres serve to deliver fragrance oils and vitamin C to the skin.  
30 Traditional methods of fragrance delivery utilize fragrance oils incorporated in alcohol, typically ethyl alcohol. These traditional carriers of fragrance oils are, by definition Volatile

Organic Compounds (VOC's) that evaporate into the air after being applied to the skin. The present invention provides a method to deliver fragrance oils and vitamin C to the skin and minimize VOC emissions. Although jojoba oils are uniquely suited for the practice of the present invention, other natural oils, whether saturated, partially saturated, or unsaturated, (through hydrogenation or transesterification), could be esterified and used in combination with the other ingredients of the compositions of the invention in less preferred embodiments. For example, cocoa oils, cocoa butter and the like (especially lipophilic materials that are already a solid at room temperature) could be used in place of or in combination with the jojoba oil, or jojoba derivatives, during esterification or other processing.

Jojoba (*Simmondsia chinensis*) is a New World crop recently domesticated and now cultivated around the world in regions with a climate similar to the Sonora Desert of Arizona and northern Mexico where jojoba originated. Jojoba oil is extracted from the seed of the female jojoba bush. The oil is found in the seed at levels normally exceeding 50% by weight but usually less than 55%. This "oil" is not a triglyceride such as sesame or almond oils, but is instead a long chain ester, typically 42 carbons in length and composed of monounsaturated fatty acids combined with monounsaturated fatty alcohols. The viscosity and appearance of jojoba oil are not unlike triglyceride oils although the tactile properties of jojoba oil render it an excellent "non oily" skin emollient. Jojoba has an unusual affinity for the skin. Unlike sesame oil or almond oil, jojoba oil is unusually resistant to oxidative degradation and rancidity. Jesuit missionaries in the southwestern USA and northern Mexico recorded the use of jojoba oil by the indigenous people of the area as a treatment for wounds and as a hair preparation.

Jojoba esters are prepared by processes described herein, which processes result in a randomized molecular combination of saturated with unsaturated jojoba fatty acids and fatty alcohols. These esters are a complex mixture of different jojoba fatty acids and fatty alcohols combined randomly and composed of differing chain lengths. The fatty acids and fatty alcohols may be either fully saturated, monounsaturated or with both the fatty alcohol and the fatty acid containing one point of unsaturation, as described above. The melting point, consistency, and physical appearance of these jojoba esters can be manipulated to produce a family of wax esters ranging from pourable liquids to hard, crystalline waxes.

The particulate dispersion of the vitamin C particles in the wax, and especially the

jojoba oil ester derivative preferred in the practice of the present invention may be effected with any form of mixing that will blend the vitamin C particles with the wax. The blending should be done in a process where the temperature of the wax, for at least a period of time allowing for good mixing, exceeds the softening temperature of the wax. It is preferred that  
5 mixing occur for a period of time where the melting temperature of the wax is exceeded. The heating may be accomplished by the direct addition of heat to the mixing environment or by the generation of heat from the mixing process. The physical mixing may, by itself, provide sufficient energy to heat the system above the softening temperature and/or above the melting temperature of the wax. Shear mixing in a kettle, mechanical blending, ultrasonic mixing,  
10 magnetically stirred masses, concrete "bowl mixers" and the like may be used, with bladed and shearing mixers generally preferred for speed and consistency. The wax and a vitamin C derivative should be chosen so that there are no chemical reactions between wax and a vitamin C form. This is easily effected with many commercially available waxes and with the preferred jojoba oil ester wax, and can be readily determined by one of ordinary skill in  
15 the art. After mixing of the two ingredients (the wax and a vitamin C), a physical separation process of the materials may be performed (e.g., dissolving the wax and removing the vitamin C particles) and the vitamin C examined to assure there has been no undesirable chemical modification thereof. The fact that the vitamin C or ascorbic acid can still be physically separated from the wax is an indication of the fact that no bonding chemical reaction has  
20 occurred between the wax and a vitamin C.

Jojoba esters are excellent carriers of fragrance oil. As fragrance oil carriers they are not prone to the development of rancidity or other unpleasant odors, resulting in delivery of the fragrance compound to consumers in a form as near that created by the perfumer as possible. The physical form of the jojoba ester and fragrance oil system can be adjusted to  
25 accommodate any type of consumer product application desired. As an example, fragrance oils can be incorporated in liquid, pourable jojoba esters that at ambient temperatures can be used by a consumer in a manner similar to the traditional use of alcohol and fragrance oil blends. Jojoba esters containing fragrance oil can be formed into spheres and these spheres subsequently incorporated into cosmetic bases with a wide range of physical and chemical  
30 properties. In this spherical form (as a discontinuous phase or dispersed phase), the jojoba esters serve to minimize the level of contact of the fragrance oil with the cosmetic base (as a

continuous phase). This is a desirable effect when the fragrance oil contains components that are not compatible with the cosmetic base, or vice versa. The particles are usually present as a dispersion of the particles in a flowable continuous phase carrying medium that is not a solvent for said particles. By flowable, it is meant that the carrying medium may be a liquid, higher viscosity fluid (such as a gel) or other material that can be spread by manual pressure in applications to the skin. The aspect of non-dissolvability of the particles within the carrying medium is desirable so that the particles do not dissolve into the carrying medium and destroy the dispersed nature of the combination. The combination may use a solvent carrier for the esters, if it is acceptable in the particular use to have the particles dissolved and the ester carried as a solute.

Individual waxes, jojoba esters or blends of the esters can be warmed to just above their melting point, the ascorbic acid incorporated, and then the molten blend poured into a jar or other dispersing package where it will solidify upon cooling, sprayed to spherodize particles, or otherwise cooled and ground to form particulates. The consistency of the blended product in the container can be adjusted to facilitate its application to the skin by use of the fingers or by a method of application using the packaging material. It is to be noted that, although the solid form is referred to as "particles", the particulate form of the composition will rapidly loses its physical particulate shape upon rubbing onto the skin, and is not a scrub agent or exfoliant because of the rapid (a few seconds) deterioration of the particulate shape when rubbed against the skin with conventional hand or finger application pressure.

The fundamental reactions used in manufacturing the preferred jojoba ester carrier phase for the ascorbic acid according to the practice of the present invention may be generally considered in the following manner. Starting materials could include:

I. The alcohol,

$R^4 - OH$  (with isopropyl alcohol (IPA,  $HO - CH - (CH_3)_2$ ) being primarily emphasized),

II. Jojoba Wax Esters,

$R^1 - COO - CH_2 - R^1$ , and

III. Fully hydrogenated Jojoba Wax Esters,

$R^2 - COO - CH_2 - R^2$ ,

wherein  $R^4$  is an alkyl group or other aliphatic group, preferably of 1 to 12 carbon atoms,

more preferably an iso-alkyl group, and most preferably an isopropyl group,

$R^1$  comprises  $CH_3 - (CH_2)_7 - CH = CH - CH_2 - (CH_2)_x -$ , and

$R^2$  comprises  $CH_3 - (CH_2)_y -$ ,

wherein x is 6, 8, 10 and/or 12, and y is 16, 18, 20 and/or 22 and

5  $R^4$  comprises  $C_nH_{2n+1}-$ , wherein n=1 to 12.

Typical product components from the preferred synthetic reactions used in the practice of the present invention with jojoba oil may include:

Partially saturated wax esters:

IV.  $R^1 - COO - CH_2 - R^2$  and/or V.  $R^2 - COO - CH_2 - R^1$ ,

10 (where isopropyl alcohol was used) isopropyl esters

VI.  $R^1 - COO - CH - (CH_3)_2$  [generically  $R^1 - COO - R^4$ ] and/or

VII.  $R^2 - COO - CH - (CH_3)_2$  [generically  $R^2 - COO - R^4$ ] and

Fatty alcohols comprising

VIII.  $R^1 CH_2 - OH$  and/or IX.  $R^2 CH_2 - OH$ .

15 The basic reactions that may be used in the preparation of the emollient compositions of the invention derived from jojoba oil may include at least the following procedures.

**Reaction A** I and II<sub>n</sub> (catalyst) → VI, VIII, and II<sub>r</sub>. This product is referred to herein as "Floraesters-IPJ" and is a liquid.

**Reaction B** I and III<sub>n</sub> (catalyst) → VII, IX, and III<sub>r</sub>. This product is referred to  
20 herein as "Floraesters-HIPJ" and is a solid.

**Reaction C** I, and II<sub>n</sub> and III<sub>n</sub> (catalyst) → IV, V, VI, VII, VIII, IX, II<sub>r</sub>, and III<sub>r</sub>. This product is referred to herein as "the broad melting range emollient" and the properties of the emollient depend upon the relative amounts of II<sub>n</sub> and III<sub>n</sub>.

The subscripts n and r respectively represent n= the naturally occurring distribution of  
25 wax esters and r= the randomized distribution of wax esters resulting from rearrangements that occur during the reactions. It is to be noted that mixing of the reaction products from A and B will give emollients with a wide range of melting points, but will not be identical to the reaction product of C because of the absence of IV and V.

A process for producing the emollient carrier may comprise the steps of:

- 30 a) providing a composition comprising jojoba oil, and or jojoba oil derivatives,  
b) adding an alcohol, e.g., having from 1 to 12 carbon atoms, to said composition,

- c) effecting alcoholysis on said jojoba oil mixed with said alcohol to produce an emollient, and
- d) effecting interesterification of remaining wax esters.

In preparing the emollient composition, the jojoba component (jojoba oil, saturated jojoba oil, partially saturated jojoba oil, unsaturated jojoba oil, or combinations thereof) is introduced into an appropriate vessel (capable of excluding air) equipped with stirring and means of heating and cooling. The jojoba components are first dried under vacuum at a temperature of 90 °C to remove most or all moisture. The anhydrous isopropyl alcohol (or other alcohol) is then added with the amount of isopropyl used being from about 20% to about 50% by weight of the jojoba component. The reactor is sealed and heat is applied to bring the temperature of the reaction mixture to about 70-75 °C. It is important that air be excluded and that the reactor be vented through a condenser to recover any unreacted alcohol.

When the temperature has reached 70-75 °C, a first addition of catalyst (e.g., a catalyst for alcoholysis and interesterification such as sodium methoxide) is made. The amount added ranges from about 0.05 or from 0.1% to about 0.6% by weight of the jojoba component with about 0.3% being preferred. After about 2 hours, a sample is taken and analyzed for the presence of the wax esters. If the wax ester content is greater than about 35% by weight, and it is desired to have a lower level of wax esters present in the reaction mixture, a second addition of catalyst is made, about 0.1% by weight of the original amount of the jojoba component. The reaction is then continued for an additional one hour. The reaction mixture is then sampled and analyzed again. If the residual wax ester content is less than 35%, the reaction may be considered to be complete. Heating is discontinued but no cooling is applied. If the reaction is considered incomplete, a third catalyst addition may be made and the reaction continued as previously described. Any remaining catalyst is neutralized and deactivated by the addition of citric acid. After about 15 minutes of agitation the neutralized catalyst (sodium citrate) is removed by filtration. Once the catalyst has been removed, any remaining isopropyl alcohol can be distilled from the product and the recovered isopropyl alcohol should be kept absolutely dry in order to be able to be used again.

As used in this description of the present invention, Floraesters 70 is **III**, Floraesters 15 is **IIr**, Floraesters 20, 30, and 60 are combinations of **IIr**, **IV**, **V**, and **IIIr**, Floraesters IPJ is a mixture of **IIr**, **VI**, and **VIII**, and Floraesters HIPJ is a combination of **IIIr**, **VII**, and **IX**.

The emollient compositions of the invention may be used alone or with additives such as fragrances and vitamin C that may impart activity to the emollient or merely aesthetics to the emollient composition to be applied.

The emolliency of jojoba is well known to those skilled in the art of cosmetic formulation. When applied to the skin, jojoba esters function as emollients to preserve and retain the natural moisture levels in the skin. Unlike volatile alcohols, jojoba esters are non-drying and in fact soften and moisturize the skin. The use of these jojoba esters as carriers for vitamin C and the delivery of fragrance oils results in a stabilized vitamin C, lower VOC emissions, a fixative effect for the fragrance oils, and also results in enhancing the moisture level and vitamin C contribution to the skin to which the jojoba esters are applied. When botanical extracts are incorporated with the jojoba esters, the esters also serve to disperse the botanicals evenly over the skin.

#### TYPICAL PROPERTIES OF JOJOBA ESTERS:

		Melting Point	Iodine Value
15	Floraesters - 70	66-70 °C	<2
	Floraesters - 60	56-60 °C	40-44
	Floraesters - 30	47-51 °C	57-61
	Floraesters - 20	42-48 °C	64-70
	Floraesters - 15	10-15 °C	78-85
20	Floraesters - IPJ	6-12 °C	75-85
	Floraesters - HIPJ	55-65 °C	<2

#### INDUSTRIAL APPLICABILITY

##### Formula 1.

	Floraesters - 60	80 grams
25	Vitamin C	10 grams
	Fragrance Oil	10 grams

This blend of Jojoba Esters, vitamin C, and fragrance oil melts at approximately skin temperature and if desired, can be formed into small spheres for direct application to the skin or for incorporation in other cosmetic base formulas.

**Formula 2.**

Floraesters - 15	55 grams
Vitamin C	10 grams
Fragrance Oil	35 grams

- 5            This blend of Jojoba Esters, vitamin C, and fragrance oil is liquid at ambient temperature and can be applied to the skin in the manner of traditional perfumes.

**Formula 3.**

Floresters - 60	65 grams
Floraesters - 70	10 grams
10 Vitamin C	10 grams
Fragrance Oil	15 grams

This blend of two Jojoba Esters, vitamin C, plus fragrance oil melts at just above skin temperature and is suitable for direct application to the skin or can first be formed into spheres for subsequent incorporation in other cosmetic bases.

15 **Formula 4.**

Floraesters - IPJ	2 grams
Floraesters - 70	18 grams
Floraesters - 60	15 grams
Vitamin C	10 grams
20 Fragrance Oil	55 grams

This blend of three Jojoba Esters, vitamin C, and fragrance oil can be formed into a soft spherical particle. Application of stronger levels of fragrance, including fragrance solubilizers, that are long lasting on the skin are possible utilizing this carrier system.

**Formula 5.**

25 Floraesters 60	60 grams
Floraesters 30	5 grams
Floraesters 70	15 grams
Vitamin C	10 grams
Fragrance Oil	9 grams
30 FD&C Red #40	1 gram

This blend of three Jojoba Esters, vitamin C, and fragrance oils is a non-flowing semi-

solid that is appropriate for direct application to the skin. A pigment has been added to increase the visual impact of the invention.

**Formula 6.**

	Floraesters 60	62 grams
5	Floraesters 70	16 grams
	Vitamin C	10 grams
	Fragrance Oil	10 grams
	Ultramarine Blue	2 grams

This blend of two Jojoba Esters, vitamin C, and fragrance oil includes a pigment  
10 selected for stability in high pH (greater than 8.0) aqueous cosmetic bases. This blend is suitable for formation into spheres and subsequent incorporation in the high pH cosmetic bases such as shower gels, facial creams, eye creams, body lotions, etc.

Other compatible cosmetic ingredients may be added to any of the above formulas to achieve different melting points, flow characteristics, water resistance, etc. Examples of other  
15 cosmetic ingredients that may be suitable for addition to the above formulas are beeswax, castor wax, carnauba wax, vegetable oils, partially hydrogenated vegetable oils, surfactants such as Tween 60™ or Tween 80™, silicone preparations, fatty alcohols, fatty acids and fatty acid esters, alpha and beta hydroxy acids, vitamins (such as vitamin E, vitamin E acetate, vitamin A palmitate, beta carotene, etc.), herbal extracts, alpha-bisabolol, conjugated linoleic  
20 acid (CLA) antioxidants such as tocopherols or mixed natural tocopherols, other antioxidants such as BHA or BHT. Pigments may also be added to any of the above to create unique visual effects. For example:

**Formula 7.**

	Floraesters 60	62 grams
25	Floraesters 70	8 grams
	Carnauba Wax	8 grams
	Vitamin C	10 grams
	Fragrance Oil	10 grams
	Red D&C #30	2 grams

30 When formed into spheres and incorporated into low pH cosmetic bases such as cosmetic pancake, this blend of Jojoba Esters, carnauba wax, vitamin C, fragrance oil and

pigment exhibits a resistance to softening and deterioration. Inclusion of the carnauba wax results in an even more dry feeling on the skin. This formula would be more appropriate as a fragrance delivery for individuals with oily skin.

#### SKIN MOISTURE DETERMINATIONS

5 The NOVA meter is an instrument designed to measure skin moisture. During a period of one week the instrument was used to determine a baseline moisture reading for an area of skin on the forearm approximately 4 inches above the wrist. Readings taken during the one-week period established the baseline at a reading of 101 units (as measured, for example, by a NOVA DPM 9003 instrument, which measures impedance or the capacitive reactance of the skin, cf. The NOVA™ Technology Corporation *Newsletter*, Summer 1997) 10 for the panelists. A higher reading indicates a more moist skin, a lower reading indicates a drier skin. The area of skin to be tested was divided laterally and marked with a pen to delineate the two skin testing areas. A control solution containing fragrance oil (35%) (Shaw Mudge M-7108) in Floraesters 15 (65%) was prepared for application to one of the skin test 15 areas. A test solution, Formula 2 in the preceding examples, containing vitamin C was prepared for application to the other skin test area. NOVA meter readings were taken in each test area 10 minutes after application of the test materials, 30 minutes after application, one hour and three hours after application. Readings were taken in triplicate and the average taken and recorded as the result below:

	<u>NOVA meter reading</u>	
	Control Solution	Vitamin C Solution Composition No. 2
20 Baseline during one week	101	101
Ten minutes after application	96	104
25 Thirty minutes after application	96	108
One hour after application	98	114
Three hours after application	98	106

Where the solvent effects of the ethanol, a component of the fragrance oil, in the control treated skin caused a decrease in the moisture content of the treated area, the vitamin 30 C treated skin exhibited an increase in skin moisture.

These and other aspects of the invention will be further described and enabled in the

practice of the following, non-limiting examples.

**EXAMPLES**

Example 1	Weight (Grams)
Floraesters 30 (jojoba ester)	50
5 Particulate vitamin C (powder form)	3

The jojoba ester and the vitamin C (approximately 5 micron particle size) were added to a high speed propeller mixing apparatus and heated to about to at least 40 °C, using high speed propeller agitation. The mixing was continued for a short period of time until the vitamin C was dispersed in the melted ester. The melted ester was formed into particles (between about 200 and 2000 microns) with particles of vitamin C dispersed therein. This process provided the particles desired in the practice of the present invention. The particles would quickly soften when applied to the skin and spread over the surface of the skin with light finger or hand pressure.

**Example 2**

15 The same example as Example 1 was repeated with a hydrocarbon wax with a melting point above 20 °C but below 60 °C. Similar mixing conditions were used and the final particulate product displayed similar results of spreading and softening upon application to the skin.

## WHAT IS CLAIMED

- 1 1. A stable composition for the delivery of a vitamin C comprising at least 5% by weight of  
2 particles of a vitamin C dispersed in a solid phase of wax that is not chemically reactive  
3 with the vitamin C, and wherein less than 1% by weight of said stable composition  
4 comprises water.
- 1 2. The composition of claim 1 wherein the stable composition is free of water.
- 1 3. The composition of claim 1 wherein said wax is a hydrocarbon wax.
- 1 4. The composition of claim 2 wherein said wax is a hydrocarbon wax.
- 1 5. A stable composition comprising at least one percent by weight of the stable composition  
2 of a vitamin C particulate ingredient and a carrier comprising a solid jojoba esters  
3 including components comprising the formulae:  
4 a)  $R^1 - \text{COO} - \text{CH}_2 - R^2$  and/or  $R^2 - \text{COO} - \text{CH}_2 - R^1$ ,  
5 b)  $R^1 - \text{COO} - R^4$  and/or  $R^2 - \text{COO} - R^4$  and  
6 c)  $R^1 - \text{CH}_2 - \text{OH}$  and/or  $R^2 - \text{CH}_2 - \text{OH}$ ,  
7 wherein  $R^4$  comprises  $\text{C}_n \text{H}_{2n+1}$ ;  $n=1$  to 12  
8  $R^1$  comprises  $\text{CH}_3 - (\text{CH}_2)_7 - \text{CH} = \text{CH} - \text{CH}_2 - (\text{CH}_2)_x -$ , and  
9  $R^2$  comprises  $\text{CH}_3 - (\text{CH}_2)_y -$   
10 wherein  $x$  is 6, 8, 10 and/or 12, and  $y$  is 16, 18, 20 and/or 22.
- 1 6. The stable composition of claim 5 wherein said composition comprises particles comprising  
2 said vitamin C in said jojoba esters.
- 1 7. The composition of claims 6 wherein said jojoba esters comprise at least 10% by weight of  
2 said particles.
- 1 8. The composition of claim 6 comprising said particles dispersed in a flowable continuous  
2 phase carrying medium that is not a solvent for said particles.

- 1 9. The composition of claim 6 comprising at least 10% by weight of a vitamin C.
- 1 10. The composition of claim 6 comprising said particles dispersed in a gel carrying medium that  
2 is not a solvent for said particles.
- 1 11. The composition of claim 6 wherein said particles comprise at least 50% by weight of said  
2 jojoba esters.
- 1 12. The composition of claim 6 wherein R<sup>4</sup> comprises an isopropyl group.
- 1 13. A cosmetic composition comprising water and the stable composition of claim 1 wherein  
2 vitamin C in said cosmetic composition displays a stability at ambient conditions of 20  
3 degrees Centigrade and 30% relative humidity of at least 90% by weight of said vitamin C  
4 remaining after 180 days.
- 1 14. A cosmetic composition comprising water and the stable composition of claim 6 wherein  
2 vitamin C in said cosmetic composition displays a stability at ambient conditions of 20  
3 degrees Centigrade and 30% relative humidity of at least 90% by weight of said vitamin C  
4 remaining after 180 days.
- 1 15. A process for stabilizing vitamin C in a topically applicable composition comprising  
2 a) heating a carrier composition comprising components of the formulae:  
3 a) R<sup>1</sup> - COO - CH<sub>2</sub> - R<sup>2</sup> and/or R<sup>2</sup> - COO - CH<sub>2</sub> - R<sup>1</sup>,  
4 b) R<sup>1</sup> - COO - R<sup>4</sup> and/or R<sup>2</sup> - COO - R<sup>4</sup> and  
5 c) R<sup>1</sup> - CH<sub>2</sub> - OH and/or R<sup>2</sup> - CH<sub>2</sub> - OH,  
6 wherein R<sup>4</sup> comprises C<sub>n</sub> H<sub>2n+1</sub>; n=1 to 12  
7 R<sup>1</sup> comprises CH<sub>3</sub> - (CH<sub>2</sub>)<sub>7</sub> - CH = CH - CH<sub>2</sub> - (CH<sub>2</sub>)<sub>x</sub> -, and  
8 R<sup>2</sup> comprises CH<sub>3</sub> - (CH<sub>2</sub>)<sub>y</sub> -  
9 wherein x is 6, 8, 10 and/or 12, and y is 16, 18, 20 and/or 22 to above a melting temperature  
10 for the composition.  
11 b) adding vitamin C to the composition, and  
12 c) cooling said carrier composition with vitamin C therein to form a solid at room  
13 temperature comprising said carrier and said vitamin C.

1 16. The process of claim 15 wherein said blend of esters comprises at least one unsaturated ester  
2 within a), b), and c) wherein:

3 a) comprises  $R^1 - \text{COO} - \text{CH}_2 - R^2$  and/or  $R^2 - \text{COO} - \text{CH}_2 - R^1$ ,

4 b) comprises  $R^1 - \text{COO} - R^4$  and/or  $R^2 - \text{COO} - R^4$ , and

5 c) comprises  $R^1 - \text{CH}_2 - \text{OH}$  and/or  $R^2 - \text{CH}_2 - \text{OH}$ ,

6 wherein  $R^4$  comprises  $\text{C}_n \text{H}_{2n+1}$ ;  $n=1$  to  $12$

7  $R^1$  comprises  $\text{CH}_3 - (\text{CH}_2)_7 - \text{CH} = \text{CH} - \text{CH}_2 - (\text{CH}_2)_x -$ , and

8  $R^2$  comprises  $\text{CH}_3 - (\text{CH}_2)_y -$

9 wherein  $x$  is 6, 8, 10 and/or 12, and  $y$  is 16, 18, 20 and/or 22.

1 17. The process of claim 16 wherein said  $R^4$  is a derivative of isopropyl alcohol.

1 18. The stable composition of claim 4 wherein the particles of wax and vitamin C have diameters  
2 between about 200 and 2000 microns and the particles of a vitamin C comprises particles of less  
3 than 10 microns.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/18392

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/48 A61K31/375 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 247 065 A (A.KOFF) 19 April 1966 (1966-04-19) claims 1,2 column 1, line 56-65	1,2,15
X	US 5 843 411 A (S.HERNANDEZ, B.SHAFFER) 1 December 1998 (1998-12-01) claims 1,16 column 4, line 48-59 column 5, line 4-11	1-4,15
X	WO 95 08322 A (MINNESOTA MINING AND MANUFACTURING) 30 March 1995 (1995-03-30) claims 1,7,8,13,14 page 7, line 3-13 page 7, line 20-22	1-4,15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

14 December 2000

Date of mailing of the international search report

21/12/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Peeters, J

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/18392

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3247065	A	19-04-1966	NONE	
US 5843411	A	01-12-1998	NONE	
WO 9508322	A	30-03-1995	US 5589194 A	31-12-1996
			DE 69419423 D	12-08-1999
			DE 69419423 T	20-01-2000
			EP 0720472 A	10-07-1996
			JP 9509356 T	22-09-1997